LIF AND SLIFR ALTERATIONS DURING RECONVALESCENCE (NOVEL CORONAVIRUS INFECTION, INFLUENZA) IN PATIENTS WITH ESSENTIAL HYPERTENSION

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Today, the analysis of the risk of developing cardiovascular complications in patients with essential hypertension (EH) following recovery from novel coronavirus infection (COVID-19) is relevant. The value of leukemia inhibitory factor (LIF) and its soluble receptor (sLIFr) in EH progression has been shown, along with the relevance of circadian approaches to assessment of the contribution of pro-inflammatory cytokines to the pathogenesis of acute cerebrovascular accidents (CVA). The study aimed to compare alterations of the LIF and sLIFr levels during reconvalescence after COVID-19 and influenza in patients with stage II EH, to determine the features that are important for the development of acute CVA, and to analyze the associations with circadian rhythms. The study was conducted in four phases (n = 180; age 55–60 years): (1) 6–8 months before COVID-19; (2–3) on day 10–14 after primary or recurrent COVID-19; (4) on day 10–14 after influenza. In each phase blood levels of LIF and sLIFr were determined by enzyme immunoassay at 7.00–8.00 h and 19.00–20.00 h, in 12 patients in four phases — at 7.00–8.00 h, 12.00–13.00 h, 19.00–20.00 h, 23.00–1.00 h throughout three days. It has been demonstrated that patients with EH show elevated LIF and sLIFr levels relative to healthy individuals in all time points (p < 0.001) and significantly elevated levels at 19.00–20.00 h (p < 0.001). The analysis of the relationship between circadian rhythms and blood levels of LIF, sLIFr in patients with stage II EH post COVID-19 and influenza has revealed similar changes in the form of the larger increase in sLIFr levels at 19.00–20.00 h (the ROC analysis data has shown predictive value for developing acute CVA within a year after COVID-19 in cases of the value increase above 7100 pg/L at 19.00–20.00 h). The principles revealed actualize further investigation of the effects of the LIF/sLIFr complex associated with the EH progression after acute infectious diseases.

Keywords: essential hypertension, LIF, sLIFr, circadian rhythms, SARS-CoV-2, influenza

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ИЗМЕНЕНИЕ LIF И SLIFR В ПЕРИОД РЕКОНВАЛЕСЦЕНЦИИ (НОВАЯ КОРОНАВИРУСНАЯ ИНФЕКЦИЯ, ГРИПП) У ПАЦИЕНТОВ С ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ

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На сегодняшний день актуален анализ риска развития сердечно-сосудистых осложнений у пациентов с гипертонической болезнью (ГБ) после перенесенной новой коронавирусной инфекции (COVID-19). Показана значимость лейкемия-ингибирующего фактора (LIF) и его растворимого рецептора (sLIFr) в прогрессировании ГБ и актуальность циркадианных подходов в оценке вклада провоспалительных цитокинов в патогенез острого нарушения мозгового кровообращения (ОНМК). Целью исследования было сопоставить изменения уровня LIF и sLIFr в период реконвалесценции после COVID-19 и гриппа у больных с ГБ II стадии, выделить значимые особенности для формирования ОНМК и проанализировать связи с циркадианными ритмами. Исследование проводили в четыре этапа (n = 180; возраст 55–60 лет): (1) за 6–8 месяцев до COVID-19; (2–3) на 10–14-й дни после первичного и повторного COVID-19; (4) на 10–14-й после гриппа. На каждом этапе определяли уровни LIF и sLIFr в крови иммуноферментным методом в 7.00–8.00 ч и 19.00–20.00 ч, 12 пациентам на четырех этапах — в 7.00–8.00 ч, 12.00–13.00 ч, 19.00–20.00 ч, 23.00–1.00 ч в течение трех суток. Показано, что у пациентов с ГБ уровень LIF и sLIFr повышен во всех временных точках по сравнению со здоровыми (p < 0,001) и заметно увеличен в 19.00–20.00 ч (p < 0,001). При анализе связи циркадианных ритмов и содержания LIF, sLIFr в крови пациентов с ГБ II стадии после COVID-19 и гриппа определены схожие изменения в виде более выраженного увеличения в 19.00–20.00 ч уровня sLIFr (данные ROC-анализа продемонстрировали предикторную ценность в отношении развития ОНМК в течение года после COVID-19 при повышении в 19.00–20.00 ч до значений более 7100 пг/мл). Выявленные принципы актуализируют дальнейшее изучение эффектов комплекса LIF/sLIFr при прогрессировании ГБ после острых инфекционных заболеваний.

Ключевые слова: гипертоническая болезнь, LIF, sLIFr, циркадианные ритмы, SARS-COV-2, грипп

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Leukemia inhibitory factor (LIF) being a member of the interleukin 6 (IL6) family has broad pleiotropic effects due to interaction with both classic IL6 receptor, gp130, and its own membrane receptor found in cardiomyocytes, neurons, endothelial cells, etc. [1]. The role of its soluble receptor, sLIFr, is still a matter of debate, since both agonist and antagonist interactions with LIF are reported. The data are provided on the correlations between the LIF/sLIFr levels and the nitric oxide metabolism products (asymmetric and symmetric dimethylarginine (ADMA, SDMA), etc.), which is significant for pathogenesis of essential hypertension (EH) [2]. A new objective was the search for factors associated with the development of complications in patients with EH in the post-COVID period, which determined introduction of new components to the design of the study focused on the cytokine mechanisms of EH progression. Today, there is limited data on alterations of the associations between the cytokine mechanisms of immune response regulation and human circadian rhythms under exposure to pathogens causing infectious diseases, including viruses [3]. At the same time, as early as in 1995 the relationship between vaccine administration and circadian rhythms of cytokine synthesis considering the significance of individual features of patients with chronic non-communicable diseases was demonstrated [4]. Russian scientific school of chronobiology has a long history of fundamental research [5, 6]. The relevance of the complex problems presented in the paper is also confirmed by the data provided in the review published in 2024, which emphasize the importance of studying the circadian control over immune-vascular interactions in both normal state and cardiovascular disorders [7]. Circadian rhythms affect both immune and vascular components of such interactions, primarily through regulation of chemotactic cytokines, adhesion of their receptors on the immune and endothelial cells, which is especially important in EH. Considering the earlier reported data on the relationship between alterations of LIF and sLIFr blood levels and concentrations of the nitric oxide metabolism products during the post-COVID period in patients with EH [2, 8], the data provided by the colleagues on the importance of circadian approaches to estimation of the contribution of pro-inflammatory cytokines to pathogenesis and outcomes of acute cerebrovascular accidents (CVA) [9], as well as information about topical presentation of membrane LIF receptors on the neurons and endothelial cells [1], we assumed significance of the dependence of the cytokine synthesis circadian rhythm alterations for EH pathogenesis. The study aimed to compare alterations of the LIF and sLIFr levels during reconvalescence after primary COVID-19 or COVID-19 re-infection and influenza in patients with stage II EH, to determine immunopathogenetic features that are important for the development of acute CVA, and to analyze the associations with circadian rhythms.

METHODS

The study was conducted at the Department of Immunology, Microbiology and Virology with a course of Clinical Immunology and Allergology of the Institute of Medicine, Ogarev Mordovia State University; the clinical phase involving patient enrollment was conducted at the Katkov Republican Clinical Hospital, vascular center of the Republican Clinical Hospital of the Republic of Mordovia No. 4 in 2019–2020 with further follow-up 2020–2024 considering the patient's place of residence.

Study design

The study included several phases of the group allocation. As a result, 12 patients out of 180 initially included patients with stage II EH underwent repeated dynamic blood collection for further investigation of the relationship between alteration of blood cytokine (LIF, sLIFr) levels and circadian biorhythms within 24 h (Fig. 1).

Phase 1. December 2019 — January–March 2020 (before the pandemic)

We enrolled 180 patients with stage II EH (80 females and 100 males) to determing morning (7:00–8:00) and evening (19:00–20:00) LIF, sLIFr concentrations, and in 40 patients of this group blood levels of cytokines were determined at four time points (7:00–8:00, 12:00–13:00, 19:00–20:00, 23:00–1:00) throughout three days.

Phase 2. May – November 2020 (circulation of the Wuhan-Hu-1 strain)

In 68 patients (30 females and 38 males) out of 180 included in the study in phase 1, the analysis of morning and evening concentrations of the same set of cytokines was conducted, and in 27 patients (10 females and 17 males) out of 68 blood levels of cytokines were determined at four time points (7:00–8:00, 12:00–13:00, 19:00–20:00, 23:00–1:00) throughout three days on days 10–14 of reconvalescence after primary COVID-19 with recording of the facts of developing cardiovascular complications (acute CVA, TIA, MI). A telephone survey was used to confirm cases of acute CVA, TIA based on medical documents within a subsequent year of follow-up, and statistically independent predictors of developing acute CVA/TIA and MI were identified (11 patients out of 68 had a history of acute CVA and TIA, two patients had a history of MI; furthermore, all 68 patients were characterized by comparable high risk of fatal and non-fatal vascular complications based on the SCORE2-OP scores).

Phase 3 — 2022–2023 (circulation of the Omicron strain)

In 24 patients (out of 27 participants of phase 2 having stage II EH and information about blood levels of cytokines collected throughout three days), blood levels of cytokines were determined at four time points (7:00–8:00, 12:00–13:00, 19:00–20:00, 23:00–1:00) throughout three days on days 10–14 of reconvalescence after COVID-19 re-infection.

Phase 4. December 2023 — March 2024 (period of increased influenza incidence)

In 12 patients out of 24 having stage II EH, who had been assessed in phase 3, blood levels of cytokines were determined at four time points (7:00–8:00, 12:00–13:00, 19:00–20:00, 23:00–1:00) throughout three days on days 10–14 of reconvalescence after influenza (type A).

Characteristics of patients

The general clinical characteristics of patients during the follow-up period confirm high comparability of the patients included in the study based on systolic blood pressure (SBP), diastolic blood pressure (DBP), average nocturnal systolic (SBPn) and diastolic (DBPn) blood pressure; body mass index (BMI), levels of low-density lipoprotein (LDL), cholesterol, creatinine, urea, glomerular filtration rate (GFR), glucose (see Appendix).

The control group included six healthy individuals matched by gender and age (three females and three males), it was

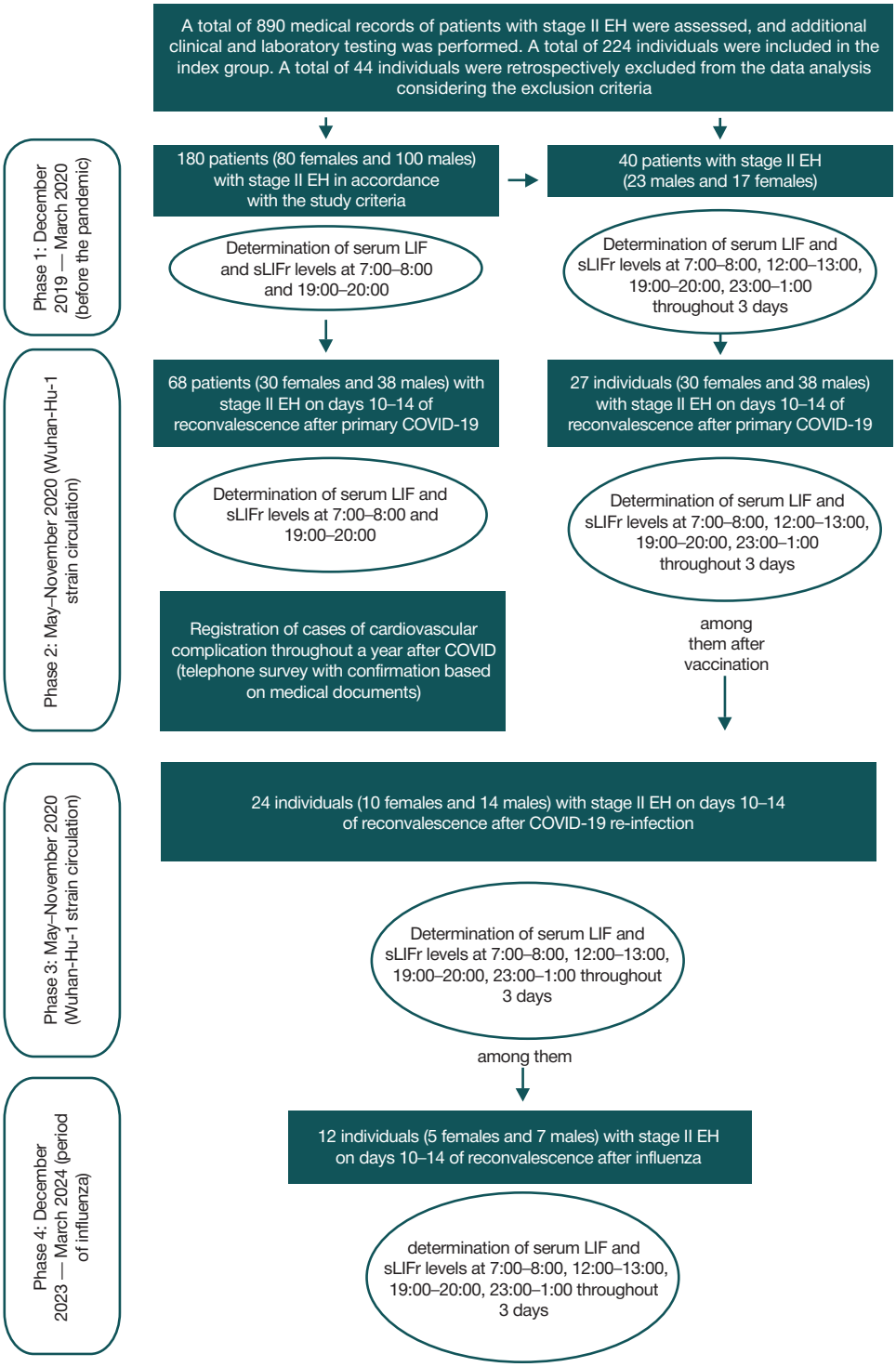

Fig. 1. Study design

formed of 32 healthy individuals included at the same time with the group of patients having EH in phase 1 for further four-phase follow-up.

The diagnosis of COVID-19 was established in accordance with the relevant temporary methodological guidelines on prevention, diagnosis, and treatment of novel coronavirus infection; moderate course of the disease and pneumonia (CT I–II) were reported in patients. The following comparable treatment regimens were used (the researchers had no influence on therapy prescription):

– primary SARS-CoV-2 infection (2020): dexamethasone 16 mg/day with dosage reduction, azithromycin 1500 mg/day, sodium heparin 10,000 IU/day;

– COVID-19 re-infection (2022–2023; moderate course, pneumonia (CT I–II)): molnupiravir 1600 mg/day since day 2–3 after the emergence of clinical manifestations in accordance with the product information, paracetamol to reduce fever up to 1000 mg/day;

– influenza (2023–2024; the diagnosis was established in accordance with the clinical guidelines of treatment of influenza in adults (2022) and confirmed by laboratory testing: immunochromatography express-test for influenza A and B viruses with confirmation by molecular genetic testing): oseltamivir 75 mg twice a day no later than three days since the emergence of initial clinical manifestations in a dose specified

Table 1. Blood levels of LIF and sLIFr (pg/mL) in patients with stage II EH on days 10–14 of reconvalescence after primary COVID-19, COVID-19 re-infection, and influenza

	7.00–8.00	19.00–20.00	
Phase 1. 6–8 months before SARS-CoV-2 infection (n = 180 individuals)			
LIF	7.18 [4.11–11.3]	12.4 [8.17–14.6]	$p < 0.001$ 7.00–8.00
sLIFr	3820 [2300-4930]	5680 [4200–7100]	$p < 0.001$ 7.00–8.00
Phase 2. Primary SARS-CoV-2 infection, 2020, Wuhan-Hu-1 strain (n = 68 individuals)			
LIF	7.29 [4.36–9.82]	12.9 [7.92–13.8]	$p < 0.001$ 7.00–8.00
sLIFr	3906 [2470–4660]	7890 [6100-8200]* phase 1	$p < 0.001$ 7.00–8.00
Phase 3. COVID-19 re-infection, 2022-2023, Omicron variant (n = 27 individuals)			
LIF	7.24 [3.69–10.9]	12.68 [8.78–13.14]*	$p < 0.001$ 7.00–8.00
sLIFr	3970 [2690–5330]	5810 [5140–6900]* phase 2	$p < 0.001$ 7.00–8.00
Phase 4. 2023-2024 (n = 12 individuals)			
LIF	6.78 [4.24–9.53]	10.9 [8.17–13.7]	$p < 0.001$ 7.00–8.00
sLIFr	4100 [2390–5900]	7600 [5560–9100]* phase 1.3	$p < 0.001$ 7.00–8.00

Note: * — $p < 0.001$ when compared with the specified phases (the Wilcoxon test was used).

in product information; paracetamol to reduce fever up to 1000 mg/day.

Inclusion criteria in 2019–2020 (phase 1)

Inclusion criteria: stage II EH; EH age of 10 years; comparable antihypertensive therapy (ACEI + thiazide/thiazide-like diuretic); age 55–60 years; concentration of the lipid metabolism indicators: total cholesterol — no more than 5.0 mmol/L, low-density lipoprotein — no more than 3.0 mmol/L, high-density lipoprotein — more than 1.0 mmol/L, triglycerides — no more than 1.7 mmol/L, thickness of the carotid artery intima media — no more than 0.9 mm, glucose levels —no more than 5.5 mg/dL, BMI — no more than 30 kg/c^2; comparable characteristics of the daily routine (sleep between 23:00 and 6:00, last meal at 20:00, no sleep disorder or the use of sleeping pills/melatonin-based drugs (these characteristics were assessed by neurologist); informed consent submitted by the patient.

Additional criteria determining inclusion of patients with stage II EH and healthy individuals in the study in 2022–2024 within the framework of allocating the index group with the analysis of circadian dependencies of blood LIF and sLIFr levels: administration of two Gam-COVID-VAC vaccine doses in 2021.

Non-inclusion criteria in 2019 and 2020–2024 (common)

Non-inclusion criteria: type 1 or 2 diabetes mellitus, allergy/autoimmune disorder, chronic infectious disease (HIV, hepatitis B and C), mental disorder, symptomatic arterial hypertension, smoking; lack of readiness for prolonged assessment; use of antihypertensive drugs, other than ACE inhibitors and/or thiazide/thiazide-like diuretics (for group with stage II EH only).

Exclusion criteria

The exclusion criteria were common: prescription of antihypertensive drugs, other than ACE inhibitors and/or thiazide/thiazide-like diuretics (for group with stage II EH only), developing acute CVA, TIA, MI or other condition determining stage III EH, autoimmune disorder diagnosed during the follow-up period, losing touch with the patient. The exclusion criteria substantiated allocation of the group of 180 patients compliant with the study criteria throughout the follow-up period.

Blood collection procedure

Blood was collected at 7:00–8:00, 12:00–13:00, 19:00–20:00, 23:00–1:00). In this study, cytokines LIF and sLIFr were isolated based on the research data on circadian patterns of human cytokine synthesis and own earlier research on the cytokine-mediated mechanisms of EH pathogenesis [6].

Blood was collected using the Vacutainer systems (BD Vacutainer, USA) (the last meal took place at least 4 h before). Blood was centrifuged for 15 min at 1500–2000 rpm. Serum was separated and stored at a temperature –30 °C for no longer than 30 days in the labeled test tubes. An interval between blood collection and freezing of blood was 60 min. The analysis was conducted by a certified specialist using the Personal Lab TM microplate analyzer (Adaltis, Italy). The following test systems were used to record serum levels of LIF and sLIFr: LIF (eBioscience (Bender MedSystems GmbH, Austria)) — the test system sensitivity was 0.66 pg/mL, the detection interval was 0.66–200 pg/mL; sLIFr (eBioscience (Bender MedSystems GmbH, Austria) — the test system sensitivity was 0.052 ng/mL, the detection interval was 0.052 –5 ng/mL.

Statistical processing of the results

Given the objectives, two software packages were used for statistical processing of the results: StatTech v. 2.8.8 (StatTech, Russia) and Stat Soft Statistica 10.0 (USA). When there were less than 50 patients (groups with assessment of six circadian points), the distribution was tested for normality using the Shapiro–Wilk test; when the number of patients exceeded 50 (groups with assessment two time points), the Kolmogorov–Smirnov test was used. Then the normally distributed quantitative indicators were described using mean values (M) and standard deviations (SD). When there was no normal distribution, the quantitative data were described using the median (Me), lower and upper quartiles (Q_1–Q_3). Given the dispersions were equal, comparison of two unrelated group based on the normally distributed quantitative trait was performed using the Student's t-test. Comparison of two unrelated group based on the non-normally distributed quantitative trait was performed using the Mann–Whitney U test. The Wilcoxon test was used for related samples (comparison of the dynamic changes in indicators in 12 patients with EH, as well as changes in six healthy individuals). The direction and strength of the correlation between two quantitative traits were assessed using the Spearman's rank

Table 2. Blood levels of LIF and sLIFr (pg/mL) in individuals without EH on days 10–14 of reconvalescence after primary COVID-19, COVID-19 re-infection, and influenza

	7.00–8.00	19.00–20.00	
Phase 1. 6–8 months before SARS-CoV-2 infection (n = 32 individuals)			
LIF	1.35 [1.09–1.73]	1.29 [1.08–1.83]	p > 0.05 7.00–8.00
sLIFr	3410 [2900–4520]	3640 [3050–4680]	p > 0.05 7.00–8.00
Phase 2. Primary SARS-CoV-2 infection. 2020. Wuhan-Hu-1 strain (n = 26 individuals)			
LIF	1.44 [1.12–1.83]	1.36 [1.02–1.79]	p > 0.05 7.00–8.00
sLIFr	3490 [2470–4660]	3720 [2200–4170]	p > 0.05 7.00–8.00
Phase 3. COVID-19 re-infection. 2022-2023. Omicron variant (n = 18 individuals)			
LIF	1.27 [1.14–1.93]	1.31 [1.18–1.42]	p > 0.05 7.00–8.00
sLIFr	3380 [2500–4720]	3460 [2700–3940]	p > 0.05 7.00–8.00
Phase 4. 2023-2024 (n = 6 individuals)			
LIF	1.42 [1.14–1.68]	1.33 [1.02–1.51]	p > 0.05 7.00–8.00
sLIFr	4070 [3710–4410]	4140 [3680–4630]	p > 0.05 7.00–8.00

correlation coefficient (when the distribution of indicators was non-normal). A predictive model characterizing the dependence of the quantitative variable on the factors was developed using the linear regression method. The ROC curve analysis method was used to assess the diagnostic value of quantitative traits when predicting certain outcomes. The quantitative trait cut-off value was determined based on the highest Youden's index value. The differences were considered significant at $p < 0.05$.

RESULTS

The results of phase 1 of the study including the data of 180 patients with stage II EH and 32 healthy individuals (the indicators obtained at 7:00–8:00 and 19:00–20:00 were analyzed) has shown that patients with stage II EH have higher ($p < 0.001$) levels of LIF and sLIFr at 7:00–8:00 and 19:00–20:00 (Table 1) compared to healthy individuals (Table 2). Furthermore, patients with EH show a significant increase in blood levels of LIF and sLIFr by 19:00–20:00 relative to the data obtained at 7:00–8:00 (by 65% (95% CI — [43–87]%) and 71.3% (95% CI — [52.8–82.1]%, respectively; $p < 0.001$), Table 1). No fluctuations of LIF and sLIFr levels during the day have been reported (Table 2).

In phase 2 of the study, in 68 patients with stage II EH and 28 patients having no EH from of phase 1 group, repeated analysis of blood LIF and sLIFr levels was performed on days 10–14 of reconvalescence after primary COVID-19 (Table 1). In patients with EH, no quantitative differences in LIF levels between the period before SARS-CoV-2 infection and early reconvalescence have been determined ($p > 0.05$). We have revealed higher sLIFr concentrations in blood of patients with stage II EH at 19:00–20:00 with growth by 92% [83–121]% when comparing with the data obtained at 7:00–8:00; the growth percentage in the evening is higher than that reported before the pandemic ($p < 0.01$) (Table 1). In individuals without EH, no differences in quantitative indicators of LIF and sLIFr

Table 3. LIF, sLIFr levels depending on the fact of developing acute CVA within a year after COVID-19 in patients with EH (2020–2021, after infection with the Wuhan SARS-CoV-2 variant)

Indicators	Acute CVA development within a year after COVID-19		p
	no	yes	
sLIFr level 7:00–8:00 (pg/mL), Me [IQR]	3469 [3128–3751]	4150.00 [3168.25; 5100.00]	0.051
sLIFr level 19:00–20:00 day 10 post COVID (pg/mL), M (SD)	5974 (853)	7352 (1197)	$p < 0.001$
LIF level 7:00–8:00 (pg/mL), Me [IQR]	7.17 [3.57–9.24]	7.36 [3.44–9.11]	$p > 0.05$
LIF level 19:00–20:00 (pg/mL), Me [IQR]	12.4 [7.49–13.9]	12.6 [7.54–14.3]	$p > 0.05$

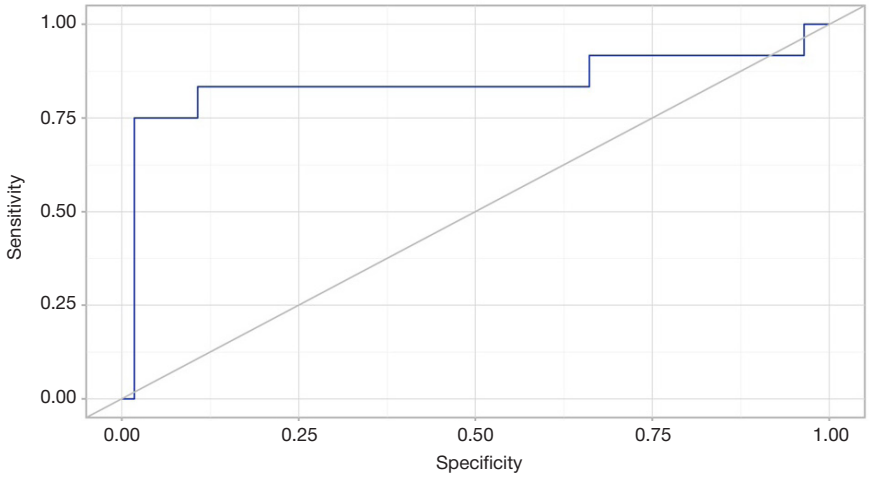

Fig. 2. ROC curve characterizing the likelihood of developing acute CVA within a year after COVID-19 as a function of sLIFr levels reported at 19:00–20:00 on days 10–14 of post-COVID period in patients with stage II EH (primary infection)

Table 4. Blood levels of LIF and sLIFr (pg/mL) in patients with stage II EH (12 individuals) on days 10–14 of reconvalescence after COVID-19, influenza, and vaccination

		7.00–8.00	12.00–13.00	19.00–20.00	23.00–01.00
1	2	3	4	5	6
6–8 months before SARS-CoV-2 infection					
LIF pg/mL	day 1	7.85 [4.51–11.9]	8.00 [4.6–12.0]	12.3 [8.12–15.2]*3.4	8.80 [4.90–10.7]*5
	day 2	7.68 [4.47–12.9]	7.96 [3.64–11]	13.2 [8.68–15.3]*3.4	9.27 [2.49–11.3]*5
	day 3	7.84 [4.30–12.2]	7.65 [3.82–11.8]	12.23 [8.39–14.3]*1.2	8.5 [3.37–10.1]*5
sLIFr pg/mL	day 1	3690 [2420–5340]	4380 [3340–4510]	5770 [4190–6750]*3.4	3090 [2460–3650]*5
	day 2	4020 [2950–5070]	3720 [3290–4970]	5480 [5070–6930]*3.4	3330 [2680–4490]*5
	day 3	4110 [2830–5610]	3660 [3340–4930]	5960 [5260–7920]*3.4	3990 [2560–4390]*5
Primary SARS-CoV-2 infection (2020, circulation of Wuhan-Hu-1 strain)					
LIF pg/mL	day 1	7.35 [4.20–10.06]	8.03 [4.67–11.56]	12.4 [8.13–14.51]*3.4	10.52 [9.75–12.5]*5
	day 2	7.05 [4.10–10.59]	7.36 [3.81–9.83	13.8 [7.54–15.5]*3.4	9.52 [8.29–11.6]*5
	day 3	7.23 [4.01–10.12]	7.95 [4.51–10.86]	13.4 [8.96–15.8]*3.4	9.88 [8.66–11.9]*5
sLIFr pg/mL	day 1	4240 [2610–4850]	3650 [2780–4810]	7540 [6400–8220]*3.4. a	3770 [2880–4370]*5
	day 2	3710 [2790–4710]	3690 [2730–4480]	7280 [5840–7550]*3.4.a	3600 [2640–3890]*5
	day 3	4140 [2780–5320]	3840 [2700–4680]	8120 [6340–8840]*3.4. a	3870 [3010–4390]*5
COVID-19 re-infection (2022–2023, circulation of Omicron strain)					
LIF pg/mL	day 1	7.15 [3.98–11.21]	7.89 [4.56–12.05]	12.68 [8.78–13.14]*3.4	7.67 [4.50–11.7]*5
	day 2	7.10 [4.00–12.95]	7.78 [4.08–11.25]	13.05 [8.48–14.98]*3.4	6.28 [4.49–12.9]*5
	day 3	7.19 [4.20–11.5]	7.64 [3.98–12.3]	13.1 [8.40–15.0]*3.4	6.59 [3.60–11.9]*5
sLIFr pg/mL	day 1	4140 [2780–5450]	4390 [3180–5240]	5790 [4830–7800]*3.4.b.d	3110 [2460–4060]*5.d
	day 2	3940 [2890–5080	3890 [3460–5110]	5520 [4930–6860]*3.4.b	3190 [2410–4080]**5
	day 3	4000 [2550–5350]	3790 [3330–5670]	5900 [5100–7200]*3.4.b	3850 [2500–4300]**5
Influenza (2023–2024)					
LIF pg/mL	day 1	6.93 [4.17–9.86]	7.14 [5.16–9.53]	11.2 [8.29–14.3]*3.4	8.77 [4.48–10.9]*5
	day 2	7.18 [4.43–9.45]	6.97 [5.48–9.11]	11.76 [8.90–14.69]*3.4	8.31 [4.80–10.14]*5.
	day 3	6.56 [3.94–10.55]	7.05 [4.80–9.27]	11.98 [7.71–14.83]*3.4	8.36 [4.17–11.66]*5
sLIFr pg/mL	day 1	3960 [2410–6200]	4160 [2730–4800]	6600 [5400–8300]*3.4.a.c	3520 [2800–4600]*5
	day 2	3890 [2260–6020]	4240 [2890–5120]	7480 [5880–9090]*3.4.a.c	3710 [2910–4830]*5
	day 3	3970 [2430–6310]	4270 [2700–4920]	7640 [5450–10300]*3.4.a.c	3470 [2770–4650]*5

Note: * — $p < 0.001$ when compared with the specified groups (3 — levels at 7:00–8:00, 4 — 12:00–13:00, 5 — 19:00–20:00, 6 — 23:00–1:00).

from the pre-COVID period were revealed ($p > 0.05$), but deviations from the results of patients with EH reported before SARS-CoV-2 infection were preserved.

In phase 2, we also started monitoring of the development of cardiovascular complications (acute CVA, TIA, and MI) in 68 patients with stage II EH throughout the year after primary COVID-19 and subsequent retrospective comparison with the morning and evening LIF and sLIFr concentrations reported on days 10–14 of reconvalescence after primary COVID-19 (Table 3). When assessing sLIFr levels reported at 7:00–8:00 depending on the acute CVA development within a year after COVID-19, we failed to find significant differences ($p = 0.051$) (Mann–Whitney *U* test was used). When assessing sLIFr levels reported at 19:00–20:00 on days 10–14 of early reconvalescence after primary COVID-19 (Wuhan-Hu-1 strain) depending on the acute CVA and TIA development within the next year, considerable differences were revealed ($p < 0.001$) (Student's t-test was used) (Table 3). The patients' LIF levels reported at 7:00–8:00 and 19:00–20:00 depending on the acute CVA and TIA development within the next year showed no differences ($p > 0.05$). When assessing the correlation between the probability of developing acute CVA or TIA and peripheral blood serum levels of sLIFr reported at 19:00–20:00 on days 10–14 post-COVID using ROC analysis, a curve was plotted (Fig. 2) (the value of 0.842 ± 0.074 corresponds to the area under the curve with the 95% CI: 0.697–0.987; $p < 0.001$). Critical elevation of sLIFr levels in blood of patients with stage II EH being through early reconvalescence after COVID-19 reported at 19:00–20:00 was 7100 pg/mL, which was identical to the maximum Youden's index value. Brain damage in patients with stage II EH was predicted, when blood sLIFr levels reported at 19:00–20:00 on days 10–14 post-COVID exceeded this value or were equal to it with sensitivity and specificity of 75% and 98.2%, respectively.

In phase 3 (after COVID-19 re-infection), assessment of morning and evening concentrations of the test cytokines showed that patterns of pre-COVID period were typical for patients with stage II EH (27 individuals) and people without EH (18 individuals), and the differences from healthy individuals were preserved ($p < 0.001$; Table 1, Table 2). No changes in the form of greater degree of sLIFr level increase at 19:00–20:00 in individuals with EH found on days 10–14 of reconvalescence after primary COVID-19 were reported for COVID-19 re-infection.

Phase 4 allowed us to assess changes in blood LIF and sLIFr levels during early reconvalescence after influenza in 12 patients with stage II EH and six individuals without EH followed-up starting from phase 1 of the study. The data obtained demonstrated trends similar to that reported after

Table 5. Blood levels of LIF and sLIFr (pg/mL) in healthy people (6 individuals) on days 10–14 of reconvalescence after COVID-19, influenza, and vaccination

		7.00–8.00	12.00–13.00	19.00–20.00	23.00–01.00
1	2	3	4	5	6
6–8 months before SARS-CoV-2 infection					
LIF pg/mL	day 1	1.32 [1.12–1.71]	1.42 [1.29–1.75]	1.26 [1.21–1.78]	1.32 [1.25–1.68]
	day 2	1.38 [1.10–1.69]	1.49 [1.31–1.80]	1.37 [1.25–1.81]	1.38 [1.26–1.70]
	day 3	1.43 [1.20–1.79]	1.56 [1.39–1.87]	1.42 [1.29–1.85]	1.43 [1.31–1.73]
sLIFr pg/mL	day 1	3890 [3100–4750]	4200 [3390–4580]	4510[3570–4870]	4210 [3800–4570]
	day 2	4100 [3260–5070]	5250 [3560–5880]	4590 [3760–5000]	4330 [3870–4650]
	day 3	3990 [3240–4880]	5070 [3450–5630]	4470 [3640–4860]	4290 [3910–4540]
Primary SARS-CoV-2 infection (2020, circulation of Wuhan-Hu-1 strain)					
LIF pg/mL	day 1	1.42 [1.14–1.68]	1.50 [1.27–1.75]	1.33 [1.02–1.51]	1.34 [1.18–1.67]
	day 2	1.22 [1.12–1.46]	1.42 [1.18–1.71]	1.37 [0.99–1.48]	1.30 [1.13–1.60]
	day 3	1.29 [1.09–1.58]	1.45 [1.24–1.68]	1.32 [0.95–1.17]	1.34 [1.10–1.53]
sLIFr pg/mL	day 1	4070 [3710–4410]	3920 [3350–4530]	4140 [3680–4630]	4260 [3650–4710]
	day 2	3970 [3460–4270]	3590 [3110–4210]	4150 [3450–4490]	3890 [3360–4440]
	day 3	3980 [3420–4350]	3950 [3180–4330]	4290 [3470–4570]	4210 [3310–4560]
COVID-19 re-infection (2022–2023, circulation of Omicron strain)					
LIF pg/mL	day 1	1.39 [1.12–1.65]	1.47 [1.25–1.72]	1.36 [1.03–1.49]	1.37 [1.16–1.64]
	day 2	1.27 [1.14–1.53]	1.49 [1.20–1.76]	1.31 [0.97–1.52]	1.34 [1.11–1.57]
	day 3	1.49 [1.18–1.85]	1.60 [1.41–1.92]	1.54 [1.27–1.83]	1.38 [1.30–1.75]
sLIFr pg/mL	day 1	3990 [3560–4340]	4040 [3180–4710]	3740 [3650–4550]	4230 [3610–4670]
	day 2	4030 [3510–4350	3860 [3170–4370]	4010 [3540–4620]	3790 [3290–4340]
	day 3	4070 [3360–4460]	3910 [2870–4170]	4130 [3560–4660]	4140 [3160–4420]
Influenza (2023–2024)					
LIF pg/mL	day 1	1.38 [1.08–1.72]	1.47 [1.31–1.72]	1.36 [0.99–1.54]	1.30 [1.15–1.63]
	day 2	1.29 [1.03–1.56]	1.36 [1.25–1.64]	1.24 [0.94–1.44]	1.20 [1.05–1.52]
	day 3	1.25 [1.06–1.55]	1.49 [1.30–1.67]	1.36 [0.97–1.22]	1.37 [1.12–1.50]
sLIFr pg/mL	day 1	4460 [3420–4600]	3730 [3160–4010]	3880 [3510–4230]	4590 [3480–4330]
	day 2	4030 [3270–4340]	3810 [3020–4270]	3790 [3530–4790]	3640 [3390–4360]
	day 3	4100 [3240–4510]	3910 [3030–4260]	4080 [3660–4700]	4010 [3150–4380]

Note: * — $p < 0.001$ when compared with the specified groups (3 — levels at 7:00–8:00, 4 — 12:00–13:00, 5 — 19:00–20:00; 6 — 23:00–1:00).

primary COVID-19 in patients with stage II EH (Table 1): more prominent sLIFr growth at 19:00–20:00 (by 91% (95% CI [81–126]%), which was higher ($p < 0.01$), than in pre-COVID period and post COVID-19 re-infection. Earlier, in 2019, we assessed blood levels of sLIFr at 7:00–8:00 and 19:00–20:00 in 60 patients with stage II EH, not included in this part of the study, but taking part in the study of the cytokine mechanisms of EH progression (the study has been going on since 2012 until now). The patients specified are comparable based on all inclusion and exclusion criteria reported in this paper for patients of four phases of follow-up. After having influenza in 2019 patients with stage II EH showed deviation of the 24-h curves from the data of the same patients reported 9–10 months before infection ($p > 0.05$): before influenza at 7:00–8:00 — 3720 [2210–4960] pg/mL, at 19:00–20:00 — 5510 [3700–6240] pg/mL; on days 10–14 of reconvalescence after influenza at 7:00–8:00 — 4140 [2640–4860] pg/mL, at 19:00–20:00 — 5680 [3380–6420] pg/mL.

Considering different size of the samples used in phases 1–4, groups were formed of 12 patients with stage II EH and six healthy individuals, in whom blood collection at four time points was performed throughout three days in all four phases of the study, in order to confirm the relationships between the patterns revealed and circadian biorhythms and to ensure higher predictive value of the differences between evening sLIFr quantitative characteristics of patients with EH and healthy individuals. Comparison of blood LIF and sLIFr levels in the specified group after primary COVID-19 in 2020 (phase 2) and COVID-19 re-infection in 2022–2023 (phase 3) caused by different SARS-CoV-2 strains confirmed the data reported for two time points: changes in 24-h dynamics of sLIFr levels in the form of more prominent increase in the evening (19:00–20:00) took place only during early reconvalescence after primary COVID-19 ($p < 0.001$; Table 4). The analysis of the data of patients with stage II EH infected with influenza A virus in fall-winter 2023–2024 revealed a 3-day trend of the increasing degree of blood sLIFr level elevation at 19:00–20:00 comparable with the reported for the period of primary SARS-CoV-2 infection during circulation of the Wuhan-Hu-1 strain. Changes in patients with EH were correlated to circadian biorhythms.

Healthy individuals showed no changes in blood LIF and sLIFr concentrations within 24 h both before COVID-19 and during reconvalescence (Table 5); the levels of LIF and sLIFr were significantly lower, than in patients with stage II EH ($p < 0.001$) and did not change during reconvalescence after influenza. No correlations with circadian rhythms were revealed in the group of healthy individuals.

DISCUSSION

The pandemic of novel coronavirus infection attracted the researchers' and clinicians' attention to the duration and features of cytokine alterations after the disease; criteria and manifestations of post-COVID syndrome are discussed. It is important to control the increasing risk of cardiovascular complications in patients with EH, and to understand the factors determining the latter. Based on the data of pre-COVID period (phase 1 of the study) our research team determined the features of patients with stage II EH in the form of higher blood concentrations of LIF and sLIFr with the upward trend observed in the evening. In 2017, we showed that growth of the LIF and sLIF levels against the background of EH was reported before prescription of antihypertensive drugs and represented a component of EH pathogenesis; when the target BP was achieved when using antihypertensive drugs, the decrease in sLIF levels was determined, there was no downward trend of LIF levels during treatment in patients with EH [2]. Regarding the fact that information about the LIF expression increase post cerebral ischemia and the neurons as the main source of LIF was published on international scientific platforms [10], the importance was substantiated of studying the relationship between this cytokine and its soluble receptor as predictors of changes in the risk of acute CVA in patients with EH, including after COVID-19, which was confirmed in phase 2 of our study. The main pool of cardiovascular complications in patients with EH reported within a year after primary COVID-19 was constituted by cases of acute CVA and TIA, and the predictor showing high sensitivity and specificity was growth of blood sLIFr levels above 7100 pg/L at 19:00–20:00 on days 10–14 of early reconvalescence. It has been earlier reported in the literature that there is balance between vasoconstrictor and vasodilator molecules affecting blood supply to the brain and enhancing the electroencephalogram power spectra, which is likely to be regulated by cytokines and related to circadian biorhythms [11]. Perhaps, this is also manifested in the relationship between blood levels of the studied cytokines against the background of hypertension and circadian biorhythms, and it is not reported in individuals with normal blood pressure. However, the question of the mechanism of sLIFr influence on the development of acute CVA and TIA remains open. If we consider sLIFr as a LIF blocking factor, then in the acute period of ischemia its increase may have protective properties, since a number of authors have noted pro-inflammatory role of LIF against the background of acute ischemic damage to neurons [10]. Then, LIF is a neurotrophic factor [10], LIF blockage via sLIFr will be perverse. These data raise new pathogenetic questions for researchers. Can a long-term LIF increase in individuals with hypertension before acute CVA act as a potential protective neurotrophic buffer that increases the resistance of neurons to damaging factors against the background of hypertension, or, conversely, support inflammatory processes, including the increased blood-brain barrier permeability? And what is the role of sLIFr, if it not only shows blocking activity against LIF, but also has its own LIF-independent immunopathogenetic effects in the form of correlation with increasing blood levels of the factors associated with the NO synthesis imbalance progression: SDMA and ADMA [2]. Microglia may be one of the points of the LIF/sLIFr effect application [12–13].

When assessing circadian rhythms of blood LIF, sLIFr levels in patients with stage II EH after COVID-19 and influenza, of greatest interest are the data on the similarity of changes in the form of the more pronounced increase in sLIFr levels at 18:00–19:00 during primary SARS-CoV-2 and after influenza. It should be noted that according to our data, no such trend following recovery from influenza has been earlier (before the pandemic) reported in patients with EH. Considering the fact that the assessment results reported after primary COVID-19 have shown the relationship between blood sLIFr levels exceeding 7100 pg/mL at 19:00–20:00 and the development of acute CVA, TIA, and that such levels are currently determined in patients with EH and post influenza, it is necessary to attract clinicians' attention to the potential group at increased risk of cardiovascular complications. It is necessary to conduct further studies involving expansion of the group followed-up during the new epidemic period, since the findings emphasize the importance of assessing circadian patterns affecting cytokine regulation of the development of acute CVA associated with EH, and the relevance of those is confirmed by the papers published by other researchers, who study the acute CVA immunopathogenesis [14].

The researchers consider the features and duration of cytokine alterations in the post-COVID period to be related specifically to primary contact of the population members with the virus, which was typical for SARS-CoV-2 in 2020. According to the data we have provided, when patients with EH were re-infected with coronavirus in 2022–2023, no earlier reported more prominent growth of sLIFr levels at 19:00–20:00 has been detected, which can be explained by leveling of the virus immune effect severity against the background of the year-round circulation, decreased virulence, and vaccination effects [15]. According to epidemiological data, the seasonal growth of influenza incidence was less prominent 2020–2022 in the context of SARS-CoV-2 predominance, which can represent the cause of the immune memory effectiveness cancellation. The lack of vaccination in the specified group of patients (submitted refusal of vaccination against influenza) has also determined formation of the "cytokine tail" with the more prominent increase in sLIFr levels post influenza as the "new infection".

The sLIFr level growth can reduce the percentage of interaction between LIF and its membrane receptor in stem cells, which can affect alteration of their differentiation into neurons, since, according to experimental data, LIF delivery to the murine brain enhances self-renewal of the neuronal stem cells in the subventricular zone and olfactory bulb with the vector of differentiation into neurons [16].

CONCLUSIONS

The LIF/sLIFr system has a significant pathogenetic component of the acute CVA and TIA development in patients with EH after novel coronavirus infection. The detected similar growth of the evening sLIFr concentrations and post influenza actualized assessment of the contribution of the broader range of viruses (SARS-CoV-2 or influenza variants) to the increase in the risk of developing acute CVA during the subsequent year in patients with EH. Chronobiology of the immune response at the macroorganism-virus interface determines the progression of non-communicable concomitant diseases and should be a part of the personalized approach to calculating the risk of developing complications by comorbid patients in the future. The demonstrated formation of the relationship between sLIFr concentration alterations and circadian biorhythms substantiates scientific and pathogenetic value of studying evening concentrations of this cytokine in patients with hypertension (between 19:00–20:00). The chronobiological patterns of this process identified open up new perspectives for assessment of the LIF/sLIFr complex effects on the EH immunopathogenesis and the development of acute CVA in the specified category of patients considering the history of viral infections (COVID-19, influenza).

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